

REPORT DOCUMENTATION P

AD-A255 286

-018E

2
STING DATA SOURCE
OTHER ASPECT OF THIS
ITEM 1215 JEFFERSON
DSC3

Public reporting burden for this collection of information is estimated to average 1 hour per gathering and maintaining the data needed, and completing and reviewing the collection of information, including suggestions for reducing this burden. To Washington DC, Davis Highway, Suite 1200, Arlington, VA 22202-4302, and to the Office of Management and

1. AGENCY USE ONLY (Leave Blank)

2. REPORT DATE

July, 1992

4. TITLE AND SUBTITLE

SOME TESTS FOR COMPARING CAUSE-SPECIFIC HAZARD RATES

5. FUNDING NUMBERS

6. AUTHOR(S)

Emad-Eldin A.A. Aly, Subhash C. Kochar and Ian W. McKeague

DAAL03-90-6-0103

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Department of Statistics
Florida State University
Tallahassee, FL 32306-3033DTIC
SELECTED

SEP 08 1992

8. PERFORMING ORGANIZATION
REPORT NUMBERFSU Technical Rpt. M-870
USARO Technical Rpt. D-127

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U. S. Army Research Office
P. O. Box 12211
Research Triangle Park, NC 27709-221110. SPONSORING/MONITORING
AGENCY REPORT NUMBER

ARO 27868.17-MA

11. SUPPLEMENTARY NOTES

The view, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

12b. DISTRIBUTION CODE

. ABSTRACT (Maximum 200 words)

ABSTRACT. We consider the competing risks problem with the available data in the form of times and causes of failure. In many practical situations (e.g. in deciding the most appropriate course of treatment for a patient) it is important to know whether the forces of two given risks are equal or whether one is "more serious" than the other. We propose some distribution-free tests for comparing their cause-specific hazard rates and cumulative incidence functions against ordered alternatives without making any assumptions on the nature of dependence between the risks. Both the censored and the uncensored cases are studied. The performance of the proposed tests is assessed in a simulation study. As an illustration we compare the risks of two types of cancer mortality (thymic lymphoma and reticulum cell carcinoma) in a strain of laboratory mice.

92

9 0 2 0 7 2

14. SUBJECT TERMS

Competing risks, ordered alternatives, cumulative incidence function, distribution-free tests, right-censored data, counting processes.

15. NUMBER OF PAGES

17

16. PRICE CODE

17. SECURITY CLASSIFICATION
OF REPORT

UNCLASSIFIED

18. SECURITY CLASSIFICATION
OF THIS PAGE

UNCLASSIFIED

19. SECURITY CLASSIFICATION
OF ABSTRACT

UNCLASSIFIED

20. LIMITATION OF ABSTRACT

UL

NSN 7540-01-280-5500

Standard Form 298 (Rev 2-89)
Prescribed by ANSI Std Z39-18
298-102

SOME TESTS FOR COMPARING CAUSE-SPECIFIC HAZARD RATES

BY EMAD-ELDIN A.A. ALY, SUBHASH C. KOCHAR AND IAN W. MCKEAGUE

University of Alberta, Indian Statistical Institute and Florida State University

July, 1992

FSU Technical Report No. M-870
USARO Technical Report No. D-127
AFOSR Technical Report No. 91-272

SOME TESTS FOR COMPARING CAUSE-SPECIFIC HAZARD RATES

Emad-Eldin A.A. Aly¹

The University of Alberta, Edmonton, Canada

Subhash C. Kochar²

Indian Statistical Institute, New Delhi, India

Ian W. McKeague³

Florida State University, Tallahassee, Florida

ABSTRACT. We consider the competing risks problem with the available data in the form of times and causes of failure. In many practical situations (e.g. in deciding the most appropriate course of treatment for a patient) it is important to know whether the forces of two given risks are equal or whether one is "more serious" than the other. We propose some distribution-free tests for comparing their cause-specific hazard rates and cumulative incidence functions against ordered alternatives without making any assumptions on the nature of dependence between the risks. Both the censored and the uncensored cases are studied. The performance of the proposed tests is assessed in a simulation study. As an illustration we compare the risks of two types of cancer mortality (thymic lymphoma and reticulum cell carcinoma) in a strain of laboratory mice.

MCS 1991 subject classifications. Primary: 62G15; Secondary: 62N05.

Key words and phrases. Competing risks, ordered alternatives, cumulative incidence function, distribution-free tests, right-censored data, counting processes.

¹ Supported by an NSERC Canada grant at the University of Alberta.

² Part of this research was done while visiting the University of Alberta supported by the NSERC Canada grant of the first author.

³ Partially supported by US Army Research Office Grant DAAL03-90-G-0103 and US Air Force Office of Scientific Research Grant AFOSR91-0048.

1. Introduction

In the competing risks model, a unit is exposed to several risks at the same time, but it is assumed that the eventual failure of the unit is due to only one of these risks which is called a 'cause of failure.' Let a unit be exposed to two risks and the notional (or latent) lifetimes of the unit under these two risks be denoted by X and Y , respectively. In general, X and Y are dependent. Also, being lifetimes, they are nonnegative. We only observe (T, δ) where $T = \min(X, Y)$ is the time of failure and $\delta = 2 - I(X \leq Y)$ is the cause of failure. Here $I(A)$ is the indicator function of the event A .

On the basis of the competing risks data it is often useful to distinguish between the following alternatives: (i) the forces of the two risks are equal, and (ii) the force of one risk is greater than that of the other, within the environment in which the two risks are acting simultaneously. Such comparisons can be made in terms of cumulative incidence functions and cause-specific hazard rates, defined as follows. The *cumulative incidence function* corresponding to cause j is

$$F_j(t) = P[T \leq t, \delta = j],$$

and the *cause-specific hazard rate* (CSHR) for cause j is

$$g_j(t) = f_j(t)/S_T(t),$$

where the F_j are assumed to have subdensities $f_j(t)$, and $S_T(t) = P[T > t] = 1 - F_1(t) - F_2(t)$ is the survival function of T . In the case when X and Y are independent, g_1 and g_2 reduce to the hazard rates corresponding to the marginal distributions of X and Y . Prentice et al. (1978) show that in general only probabilities expressible as functions of g_1 and g_2 may be estimated from the observable data (T, δ) .

We mention two practical examples in which it is important to be able to make comparisons between cause-specific hazard rates (as well as cumulative incidence functions). The first example arises in reliability testing. Suppose that either of two components in a series system can be replaced to improve overall system reliability. One would replace the second component in preference to the first if $g_1 < g_2$ or $F_1 < F_2$. The second example, this one biomedical, comes from a paper of Benichou and Gail (1990). It concerns time to cancer recurrence in patients

or	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
by Codes			
Dist	Avail	and/or	Special
A-1			

with surgically resected cancer. In deciding whether to give a toxic therapy in the hope of preventing cancer recurrence it is appropriate to compare the cumulative incidence function for cancer recurrence (Benichou and Gail call this the absolute risk of recurrence), F_1 , and the cumulative incidence function for other risks (e.g. other causes of death), F_2 . A physician would be reluctant to recommend a toxic cancer treatment in an elderly patient in whom $F_1 < F_2$ or $g_1 < g_2$. Benichou and Gail go on to discuss the importance of the concept of absolute risk in evaluating public health measures to prevent disease. Gray (1988) also draws attention to the usefulness of comparing cause-specific incidence for different types of failure.

In this article we propose some methods for comparing CSHR's and cumulative incidence functions. Our tests are less subjective than graphical procedures based on inspections of estimates of the CSHR's themselves. We are interested in testing the hypotheses

$$H_1 : g_1(t) \leq g_2(t), \quad t \geq 0$$

$$H_2 : F_1(t) \leq F_2(t), \quad t \geq 0$$

with strict inequalities for some t . These hypotheses represent different ways of saying that risk Y is "more serious" than risk X . Clearly H_1 implies H_2 . We regard H_1 and H_2 as alternatives to the null hypothesis of equal risks:

$$H_0 : g_1(t) = g_2(t), \quad t \geq 0.$$

Note that there is often no reason to expect *a priori* that the cause specific risks g_1 and g_2 are equal (except, say, when g_1 and g_2 represent two identical components in a series system), but this is the natural choice of null hypothesis against which the ordered alternatives H_1 and H_2 should be tested. A similar choice of null hypothesis is made in the two-sample survival analysis problem when testing whether survival in one group is better than survival in another group, cf. Pepe and Fleming (1989).

In the case that X and Y are *independent*, Bagai, Deshpandé and Kocher (1989 a,b) proposed distribution-free tests for testing the equality of two competing risks against stochastic ordering and failure rate ordering. Sen (1979) proposed nonparametric tests with maximum asymptotic relative efficiency for interchangeability of the competing risks against alternatives specified in terms of $P[\delta = j | T = t]$. Aras and Deshpandé (1989) proposed locally most powerful rank tests for testing H_0 against various parametric alternatives expressed in terms of F_1 and F_2 .

The remainder of the paper is organized as follows. In Section 2 we consider the problem of testing the null hypothesis of equality of CSHR's against the alternatives specified by H_1 and H_2 . Our tests are of Kolmogorov-Smirnov type and are distribution-free. Formulae for the exact null distributions of the test statistics are provided. The asymptotic distributions are also derived. In Section 3 we consider an extension of our tests to deal with right-censored data. The results of a simulation study and an example are discussed in Section 4. In Section 5 we describe another extension of our tests to allow comparisons on any given time interval.

2. Testing for the equality of CSHR's against ordered alternatives

In this section we introduce our tests for H_1 and H_2 in the uncensored case. The tests are based on the competing risk data $\{(T_i, \delta_i); i = 1, \dots, n\}$ for n independent and identical units.

2.1 Testing H_0 against H_1 . A distribution-free test of H_0 vs. H_1 can be constructed using the fact that, under H_1 , the function $\psi(t) = F_1(t) - F_2(t)$ is nonincreasing in t . This is a consequence of the identity $F_j(t) = \int_0^t g_j(u) S_T(u) du$ and provides a rationale for the test statistic

$$D_{1n}^+ = \sup_{0 \leq s < t < \infty} \{0, \psi_n(s) - \psi_n(t)\},$$

where $\psi_n(t) = F_{1n}(t) - F_{2n}(t)$. Here $F_{jn}(t) = n^{-1} \sum_{i=1}^n I\{\delta_i = j, T_i \leq t\}$ is the empirical estimator of F_j . Positive values of D_{1n}^+ provide evidence that g_2 is larger than g_1 in some interval. Note that

$$\begin{aligned} D_{1n}^+ &= \max_{0 \leq i < j \leq n} \frac{1}{n} \left\{ 0, j - i - 2 \sum_{\ell=i+1}^j W_\ell \right\} \\ &= \max_{0 \leq i < j \leq n} \frac{1}{n} \left\{ 0, \sum_{\ell=i+1}^j \eta_\ell \right\} \\ &= \max_{0 \leq i < j \leq n} \frac{1}{n} \left\{ 0, Z_j - Z_i \right\}, \end{aligned} \tag{2.1}$$

where

$$W_i = \begin{cases} 1 & \text{if } \delta \text{ corresponding to } T_{(i)} \text{ (the } i\text{th ordered } T_i\text{) is 1} \\ 0 & \text{otherwise,} \end{cases}$$

$\eta_i = 1 - 2W_i$, $i = 1, 2, \dots, n$, $Z_0 = 0$ and $Z_k = \eta_1 + \dots + \eta_k$, $k = 1, 2, \dots, n$.

To obtain the exact null distribution of D_{1n}^+ we argue as follows. Kochar and Proschan (1991) proved that T and δ are independent under H_0 . Consequently, under H_0 , W_1, \dots, W_n are i.i.d. Bernoulli random variables with $P(W_i = 0) = P(W_i = 1) = \frac{1}{2}$ and η_1, \dots, η_n are i.i.d. with $P(\eta_i = -1) = P(\eta_i = 1) = \frac{1}{2}$. It follows, using Simons (1983), that

$$P\{nD_{1n}^+ < t\} = P\{-t < \min_{0 \leq j \leq n} Z_j < \max_{0 \leq j \leq n} Z_j < t + 1\}, \quad (2.2)$$

cf. Aly, Gombay and Kochar (1992, proof of Theorem 3.1 (i)). By applying Csáki (1986, (2.6)), this yields an exact formula for the null distribution function of D_{1n}^+ . The asymptotic null distribution can be obtained from (2.1) and the discussion preceding (2.2) by using the invariance principle for partial sums (see, for example, Chapter 2 of Csörgő and Révész (1981)). We summarize this discussion in the following theorem.

THEOREM 2.1. *Under H_0*

$$\begin{aligned} P\{nD_{1n}^+ < t\} &= \frac{2}{2t+1} \sum_{j=0}^{2t} \left\{ \cos \frac{j\pi}{2t+1} \right\} \sin \left\{ \frac{j\pi(t+1)}{2t+1} \right\} \left\{ 1 + \cos \frac{j\pi}{2t+1} \right\} \\ &\quad \times \left\{ \frac{1 - (-1)^j}{2} \right\} / \sin \frac{j\pi}{2t+1} \end{aligned} \quad (2.3)$$

for $t = 1, \dots, n+1$, and

$$\sqrt{n}D_{1n}^+ \xrightarrow{\mathcal{D}} \sup_{0 \leq x \leq 1} |W(x)|$$

where $\{W(t), t \geq 0\}$ is a standard Brownian motion. Consequently, for $c > 0$

$$P\{\sqrt{n}D_{1n}^+ \leq c\} \rightarrow \frac{4}{\pi} \sum_{k=0}^{\infty} \frac{(-1)^k}{2k+1} \exp\{-\pi^2(2k+1)^2/8c^2\}. \quad (2.4)$$

The exact formula (2.3) can be used to generate a table of critical values, see Aly, Gombay and Kochar (1992). Using (2.4) the asymptotic 0.90, 0.95 and 0.99 quantiles of $\sqrt{n}D_{1n}^+$ are found to be 1.96, 2.241 and 2.807, respectively.

2.2 Testing H_0 against H_2 . Since under H_2 , $\psi(t)$ is nonpositive, a natural test statistic for testing H_0 against H_2 is given by

$$D_{2n}^+ = \sup_{0 \leq t < \infty} \{0, -\psi_n(t)\}.$$

We reject H_0 for large values of D_{2n}^+ . Note that D_{2n}^+ can be written as $\max_{0 \leq j \leq n} Z_j$, where Z_0, Z_1, \dots, Z_n are as in (2.1). Thus, by Lemma 4.8.1 of Rényi (1970),

$$P\{nD_{2n}^+ = k\} = \frac{1}{2^n} \binom{n}{[\frac{n-k}{2}]}, \quad k = 0, 1, 2, \dots, n$$

under H_0 . This gives the exact null distribution of D_{2n}^+ . The asymptotic null distribution is obtained using the invariance principle for partial sums: under H_0

$$P\{\sqrt{n}D_{2n}^+ > x\} \rightarrow P\{\sup_{0 \leq t \leq 1} W(t) > x\} = 2(1 - \Phi(x)), \quad x \geq 0,$$

where Φ is the standard normal distribution function.

3. Censored data

In this section we consider an extension of our tests to allow for the possibility of right-censoring. The underlying censoring mechanism will be represented by a censoring time C which is assumed independent of the latent failure times X and Y . Denote the survival function of C by S_C and assume that $S_C(t) > 0$ for all t .

Under right-censoring we observe n iid copies, $(\tilde{T}_i, \tilde{\delta}_i)$, $i = 1, \dots, n$, of $\tilde{T} = \min(T, C)$ and $\tilde{\delta} = \delta I(T \leq C)$. Our approach is to look for a suitable modification of the function ψ . Recall that $\psi(t) = \int_0^t S_T(u-) (g_1(u) - g_2(u)) du$. In order to obtain distribution-free tests of H_1 and H_2 in the censored case, look at the function

$$\phi(t) = \int_0^t S_T(u-) S_C(u-)^{1/2} (g_1(u) - g_2(u)) du.$$

The factor $S_C(u-)^{1/2}$ turns out to be precisely what is needed to compensate for the censoring. We have that $\phi(t)$ nonincreasing under H_1 and identically zero under H_0 , so to test H_0 against H_1 it is natural to use the test statistic

$$D_{3n}^+ = \sup_{0 \leq s < t < \infty} \{0, \phi_n(s) - \phi_n(t)\},$$

where ϕ_n is a suitable estimator of ϕ . Similarly,

$$D_{4n}^+ = \sup_{0 \leq t < \infty} \{0, -\phi_n(t)\},$$

can be used to test H_0 against H_2 . An obvious choice of ϕ_n is

$$\phi_n(t) = \int_0^t \hat{S}_T(u-) \hat{S}_C(u-)^{1/2} d(\hat{\Lambda}_1 - \hat{\Lambda}_2)(u),$$

where \hat{S}_T and \hat{S}_C are the product-limit estimators of S_T and S_C , and $\hat{\Lambda}_j$ is the Aalen estimator of the cumulative CSHR function $\Lambda_j(t) = \int_0^t g_j(u) du$:

$$\hat{\Lambda}_j(t) = \sum_{i: \tilde{T}_i \leq t} I(\tilde{\delta}_i = j) / R_i$$

where $R_i = \#\{k : \tilde{T}_k \geq \tilde{T}_i\}$ is the size of the risk set at time \tilde{T}_i .

We note that $\hat{\Lambda}_j$ is a special case of an estimator discussed by Aalen and Johansen (1978) in connection with estimation of the transition probabilities of a non-homogeneous Markov chain with finitely many states. Indeed, we are dealing with a three-state non-homogeneous Markov chain having two absorbing states corresponding to the two types of failure.

The following result, proved in the Appendix, shows that D_{3n}^+ and D_{4n}^+ are asymptotically distribution-free and have the same limiting distributions they do in the uncensored case.

THEOREM 3.1. Under H_0

$$\sqrt{n}D_{3n}^+ \xrightarrow{\mathcal{D}} \sup_{0 \leq x \leq 1} |W(x)| \quad \text{and} \quad \sqrt{n}D_{4n}^+ \xrightarrow{\mathcal{D}} \sup_{0 \leq x \leq 1} W(x).$$

Our approach easily extends to the case of multiple (rather than just two) competing risks in which any two of the cause-specific risks are to be compared. No structure needs to be imposed on the dependency between the multiple risks, although the corresponding latent failure times need to be independent of the censoring, as before. Let T be the minimum of a finite collection of latent failure times which include X and Y , and let \mathcal{E} denote the corresponding cause of failure. Extensions of D_{3n}^+ and D_{4n}^+ that preserve the above asymptotic distributions are obtained by using $\phi_n(t)/\sqrt{p_n}$ in place of $\phi_n(t)$, where

$$p_n = \int_0^\infty \hat{S}_T(u-) d(\hat{\Lambda}_1 + \hat{\Lambda}_2)(u)$$

is a consistent estimator of $P[\delta = 1 \text{ or } 2]$, see the Appendix.

4. Simulation results and an example

Our test procedures are consistent against their respective alternatives, H_1 or H_2 . However, we would like to know whether they are powerful enough for practical applications. For that purpose, we carried out a simulation study, and the results show that our tests are readily able to detect these ordered alternatives.

For the distribution of (X, Y) we used Block and Basu's (1974) absolutely continuous bivariate exponential (ACBVE) distribution having density

$$f(x, y) = \begin{cases} \frac{\lambda_1 \lambda (\lambda_2 + \lambda_0)}{\lambda_1 + \lambda_2} e^{-\lambda_1 x - (\lambda_2 + \lambda_0)y} & \text{if } x < y \\ \frac{\lambda_2 \lambda (\lambda_1 + \lambda_0)}{\lambda_1 + \lambda_2} e^{-\lambda_2 y - (\lambda_1 + \lambda_0)x} & \text{if } x > y \end{cases}$$

where $(\lambda_0, \lambda_1, \lambda_2)$ are parameters and $\lambda = \lambda_0 + \lambda_1 + \lambda_2$. The CSHR's are given by

$$g_j(t) = \frac{\lambda_j \lambda}{\lambda_1 + \lambda_2},$$

so H_1 holds if and only if $\lambda_1 < \lambda_2$. Under this model H_1 and H_2 are equivalent. The parameter λ_0 controls the degree of dependence between X and Y ; they are independent if and only if $\lambda_0 = 0$. We set $\lambda_1 = 1$ and considered various higher values of λ_2 corresponding to larger and larger departures from H_0 . The censoring was taken to be exponential with parameter values 1 and 3, corresponding to "light" and "heavy" censoring (about 25% and 50% censored, respectively). For the sake of comparison we included results for the uncensored case as well. We used asymptotic critical levels of 5%.

Inspection of Table 1 shows that use of the asymptotic critical levels gives somewhat conservative tests, and this effect increases as the censoring becomes more severe. The test based on D_{3n}^+ appears to be more conservative than the one based on D_{4n}^+ . However, the tests become less conservative as the sample size increases (in fact we have found that the levels of the tests are close to their nominal 5% values for sample sizes over 500, even under heavy censoring). There is no apparent adverse effect on the levels or the power due to lack of independence of X and Y . (Pearson's correlation between X and Y is about .15 for the table entries corresponding to $\lambda_0 = 1$.)

As an application we have analyzed a set of mortality data given in Hoel (1972). These data were obtained from a laboratory experiment on 99 RMF strain male mice which had received a radiation dose of 300 rads at 5-6 weeks of age and were kept

in a conventional laboratory environment. The cause of death was classified into thymic lymphoma, reticulum cell sarcoma, and other causes. For us, "other causes" represents censoring (39% were censored), and the two types of cancer mortality are taken to be the two causes of failure that we wish to compare, i.e. g_1 and g_2 are the CSHR's from lymphoma and sarcoma respectively. Our analysis depends on the assumption that the two diseases are lethal and independent of other causes of death, but we do not need to assume that they are independent of one another.

[Insert Figures 1 and 2 about here]

Figure 1. Aalen estimates of cumulative CSHR's for lymphoma (dashed line) and sarcoma (solid line).

Figure 2. Plot of $\sqrt{n}\phi_n(t)$ (solid line) and the asymptotic 5% critical levels for D_{4n}^+ (dashed lines).

We obtained $D_{3n}^+ = 4.81$, which gives a P -value of less than .01 for testing H_0 against H_1 . Also, $D_{4n}^+ = 2.77$, which gives a P -value of .0056 for testing H_0 against H_2 . When the roles of lymphoma and sarcoma were reversed, we obtained $D_{3n}^+ = D_{4n}^+ = 2.03$, so the P -values for the two tests are close to .1 and .05 respectively.

Our conclusion is that the two cause-specific hazard rates are unequal. Note that we cannot conclude that the CSHR for sarcoma is *uniformly* larger than the CSHR for lymphoma; the large value $D_{3n}^+ = 4.81$ only indicates that the sarcoma CSHR is larger than the lymphoma CSHR in *some* age interval. Indeed, inspection of a plot of the two cumulative CSHR estimates (Figure 1) suggests that up to 500 days there is moderate risk of lymphoma, yet negligible risk of sarcoma. After 500 days the situation reverses: there is negligible risk of lymphoma but high risk of sarcoma, and it is this large difference that the test statistic D_{3n}^+ is picking up. This is also reflected in the plot of $\sqrt{n}\phi_n(t)$ in Figure 2. Such plots are useful in avoiding misinterpretation of the test statistics. Plots of estimates of the CSHR's themselves are also useful; these can be made by finding smoothed derivatives of the cumulative CSHR estimates, see Ramlau-Hansen (1983), and are somewhat easier to interpret than plots of the cumulative CSHR estimates. However, our tests offer a less subjective comparison of CSHR's than can be made from a simple visual inspection of such plots.

5. Comparing CSHR's in $[t_1, t_2]$

It is often useful to compare CSHR's (or cumulative incidence functions) in a given time interval $[t_1, t_2]$, rather than at all times. For instance, an examination of plots of the cumulative CSHR estimates for Hoel's data strongly suggests that the CSHR for sarcoma is much larger than the CSHR for lymphoma after 500 days. In the second example discussed in the Introduction, Benichou and Gail (1990, p. 820) are interested in comparing the CSHR for cancer recurrence with the CSHR for other risks at times between one and five years following surgical treatment.

It is straightforward to generalize our tests in Section 3 to deal with such cases. We want a test of

$$H_0^* : g_1(t) = g_2(t), \quad t_1 \leq t < t_2$$

against the alternative

$$H_1^* : g_1(t) \leq g_2(t), \quad t_1 \leq t < t_2$$

with strict inequality for some $t \in [t_1, t_2]$. We replace ϕ by the function

$$\phi^*(t) = (S_T(t_1) - S_T(t_2))^{-1/2} \int_{t_1}^t S_T(u-) S_C(u-)^{1/2} (g_1(u) - g_2(u)) du.$$

Clearly H_1^* is equivalent to ϕ^* nonincreasing on $[t_1, t_2]$. As before, we suggest the test statistic

$$D_{5n}^+ = \sup_{t_1 \leq s < t \leq t_2} \{0, \phi_n^*(s) - \phi_n^*(t)\},$$

where $\phi_n^*(t)$ is obtained by substituting \hat{S}_T etc. into ϕ^* . It can be shown by routine modifications of the proof of Theorem 3.1 that $\sqrt{n}D_{5n}^+$ converges in distribution to $\sup_{0 \leq x \leq 1} |W(x)|$ under H_0^* .

When this test was applied to Hoel's data, we obtained the highly significant values of $D_{5n}^+ = 5.56$ (resp. 3.69) when testing whether the CSHR for sarcoma is larger (resp. smaller) than the CSHR for lymphoma after (resp. before) 500 days. This confirms our earlier conjectures arising from examination of Figures 1 and 2.

APPENDIX

PROOF OF THEOREM 3.1. Suppose we can show that

$$\sqrt{n}\phi_n \xrightarrow{\mathcal{D}} W(F_T(\cdot)). \quad (A.1)$$

Then, the second part of the theorem is clear. Using the continuous mapping theorem,

$$\begin{aligned} \sqrt{n} \sup_{0 \leq s < t < \infty} \{ \phi_n(s) - \phi_n(t) \} &\xrightarrow{\mathcal{D}} \sup_{0 \leq s < t < \infty} \{ W(F_T(s)) - W(F_T(t)) \} \\ &\xrightarrow{\mathcal{D}} \sup_{0 \leq u < v \leq 1} \{ W(u) - W(v) \} \\ &\xrightarrow{\mathcal{D}} \sup_{0 \leq u \leq 1} \{ W(u) - \inf_{0 \leq v \leq u} W(v) \}. \end{aligned}$$

The statement of the first part of the theorem now follows by

$$W(u) - \inf_{0 \leq v \leq u} W(v) \xrightarrow{\mathcal{D}} \sup_{0 \leq v \leq u} W(v) - W(u)$$

and the following well known result of Lévy (1948):

$$\sup_{0 \leq v \leq u} W(v) - W(u) \xrightarrow{\mathcal{D}} |W(u)|,$$

see Chung and Williams (1983). It remains to prove (A.1), for which we use the counting process approach developed by Aalen (1978). Note that we can write $\hat{\Lambda}_j$ in the form

$$\hat{\Lambda}_j(t) = \int_0^t \frac{d\bar{N}_j(u)}{\bar{Y}(u)},$$

where $1/0 \equiv 0$.

$$\begin{aligned} \bar{Y} &= \sum Y_i, \quad \bar{N}_j = \sum N_{ij}, \\ Y_i(u) &= I(\tilde{T}_i \geq u), \quad N_{ij}(u) = I(\tilde{T}_i \leq u, \tilde{\delta}_i = j), \end{aligned}$$

for $j = 1, 2$, and the summations are over $i = 1, \dots, n$. Let

$$M_{ij}(t) = N_{ij}(t) - \int_0^t Y_i(u) d\Lambda_j(u).$$

Then $M_{ij}, i = 1, \dots, n$ are orthogonal martingales under the natural filtration generated by the above processes. Let $\bar{M}_j = \sum M_{ij}$. The predictable variation process of \bar{M}_j is $\int_0^t \bar{Y}(u) d\Lambda_j(u)$. By $P(X = Y) = 0$, the counting processes \bar{N}_1 and \bar{N}_2 almost surely have no simultaneous jumps, so \bar{M}_1 and \bar{M}_2 are orthogonal martingales (this is a standard result from counting process theory). Thus, the predictable variation process of $\bar{M}_1 - \bar{M}_2$ is $\int_0^t \bar{Y}(u) d\Lambda_0(u)$, where $\Lambda_0 = \Lambda_1 + \Lambda_2$. Under H_0

$$\phi_n(t) = \int_0^t \frac{\hat{S}_T(u-) \hat{S}_C(u-)^{1/2}}{\bar{Y}(u)} d(\bar{M}_1 - \bar{M}_2)(u).$$

Since $\hat{S}_T(u-)$ and $\hat{S}_C(u-)$ are left continuous and adapted, they are predictable, so $\sqrt{n}\phi_n$ is a martingale with predictable variation process

$$\int_0^t \frac{\hat{S}_T(u-)^2 \hat{S}_C(u-)}{\bar{Y}(u)/n} d\Lambda_0(u).$$

By the Glivenko-Cantelli theorem, $\bar{Y}(u)/n$ converges uniformly in u to $P(\tilde{T} \geq u) = S_T(u-)S_C(u-)$ almost surely. Hence, by the uniform consistency of the product-limit estimator on $[0, t]$, the above variation process converges in probability to $\int_0^t S_T(u-) d\Lambda_0(u) = F_T(t)$. Here we have used the fact that the cumulative hazard function of T is Λ_0 ; see Prentice et al. (1978). The appropriate Lindeberg condition is easily checked. (A.1) follows by Rebolledo's (1980) martingale convergence theorem. \square

We conclude by indicating how to extend the above proof to deal with multiple competing risks. In this setting the predictable variation process of $\sqrt{n}\phi_n$ converges in probability to $F_1 + F_2$. Since p_n is consistent for $P[\delta = 1 \text{ or } 2]$, it follows that

$$\sqrt{\frac{n}{p_n}} \phi_n \xrightarrow{\mathcal{D}} W(F_{12}(\cdot)),$$

where F_{12} is the conditional distribution function of $\min(X, Y)$ given that $\delta = 1$ or 2. This extends (A.1). The remaining steps of the proof are identical.

References

Aalen, O. O. (1978). Nonparametric inference for a family of counting processes. *Ann. Statist.* **6** 701-726.

Aly, E.-E., Gombay, E. and Kocher, S. (1992). On testing the symmetry of a distribution against positive biasedness. Tech. Rep., University of Alberta, Edmonton.

Aalen, O. O. and Johansen, S. (1978). An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scand. J. Statist.* **5** 141-150.

Aras, G. and Deshpandé, J. V. (1989). Statistical analysis of dependent competing risks. Tech. Rep. No. 90, Univ. of California, Santa Barbara. To appear in *Statistics and Decisions*.

Bagai, I., Deshpandé, J. V. and Kochar, S. C. (1989a). A distribution-free test for the equality of failure rates due to two competing risks. *Commun. Statist. Theor. Meth.* **18** 107-120.

Bagai, I., Deshpandé, J. V. and Kochar, S. C. (1989b). Distribution-free tests for stochastic ordering among two independent risks. *Biometrika* **76** 775-778.

Benichou, J. and Gail, M. H. (1990). Estimates of absolute cause-specific risk in cohort studies. *Biometrics* **46** 813-826.

Block, H. W. and Basu, A. P. (1974). A continuous bivariate exponential extension. *J. Amer. Statist. Assoc.* **69** 1031-1037.

Chung, K. L. and Williams, R. J. (1983). *Introduction to Stochastic Integration*. Birkhauser, Basel.

Csáki, E. (1986). Some applications of the classical formula on ruin probabilities. *J. Statist. Plann. Inference* **14**, 35-42

Csörgő, M. and Révész, P. (1981). *Strong Approximations in Probability and Statistics*. Academic Press, New York.

Friday, D. S. and Patil, G. P. (1977). A bivariate exponential model with applications to reliability and computer generation of random variables. *The Theory and Applications of Reliability*, Vol. 1, pp. 527-549, edited by C. P. Tsokos and I. N. Shimi, Academic Press.

Gray, R. J. (1988). A class of k -sample tests for comparing the cumulative incidence of a competing risk. *Ann. Statist.* **16** 1141-1154.

Hoel, D. G. (1972). A representation of mortality data by competing risks. *Biometrics* **28**, 475-488.

Kochar, S. C. and Proschan, F. (1991). Independence of time and cause of failure in the dependent competing risks model. *Statistica Sinica* **1**, 295-299.

Lévy, P. (1948). *Processus Stochastiques et Mouvement Brownien*. Gauthier-Villars, Paris.

Marsaglia, G., Zaman, A. and Tsang, W. W. (1990). Toward a universal random number generator. *Statistics and Probability Letters* **8** 35-39.

Pepe, M. S. and Fleming, T. R. (1989). Weighted Kaplan-Meier statistics: a class of discrete tests for censored survival data. *Biometrics* **45** 497-507.

Prentice, R. L., Kalbfleisch, J. D., Peterson, A. V., Flourney, N., Farewell, V. T. and Breslow, N. E. (1978). The analysis of failure times in the presence of competing risks. *Biometrics*, **34**, 541-554.

Ramlau-Hansen, H. (1983). Smoothing counting process intensities by means of kernel functions. *Ann. Statist.* **11** 453-466.

Rebolledo, R. (1980). Central limit theorems for local martingales. *Z. Wahrsch. verw. Gebiete* **51** 269-286.

Rényi, A. (1970). *Foundations of Probability*, Holden-Day, London.

Sen, P. K. (1979). Nonparametric tests for interchangeability under competing risks. *Contributions to Statistics - J. Hajek Memorial Volume*, J. Jurekova, Ed. Reidel, Dordrecht.

Simons, G. (1983). A discrete analogue and elementary derivation of 'Lévy's equivalence' for Brownian motion. *Statist. Probab. Letters* **1** 203-206.

Table 1. Observed levels and powers of tests for equality of CSHR's based on D_{3n}^+ (resp. D_{4n}^+) at an asymptotic level of 5%. The underlying distribution of (X, Y) is Block and Basu's (1974) ACBVE with $\lambda_1 = 1$.

(b) Uncensored

λ_2	$n = 50$		$n = 100$	
	$\lambda_0 = 0$	$\lambda_0 = 1$	$\lambda_0 = 0$	$\lambda_0 = 1$
1.0	3.86 (4.90)	3.86 (4.90)	3.68 (4.44)	3.69 (4.44)
1.5	32.37 (39.46)	32.38 (39.46)	54.41 (61.05)	54.43 (61.05)
2.0	67.46 (74.95)	67.46 (74.95)	92.59 (95.11)	92.59 (95.11)
2.5	87.66 (91.96)	87.66 (91.96)	99.4 (99.78)	99.40 (99.78)

(b) Lightly censored (18%-33%)

λ_2	$n = 50$		$n = 100$	
	$\lambda_0 = 0$	$\lambda_0 = 1$	$\lambda_0 = 0$	$\lambda_0 = 1$
1.0	2.89 (3.64)	2.98 (3.87)	3.45 (4.16)	3.37 (4.06)
1.5	21.95 (27.64)	24.19 (30.00)	41.32 (47.97)	44.86 (51.22)
2.0	51.95 (60.52)	55.40 (63.64)	83.31 (87.64)	85.57 (89.76)
2.5	76.35 (82.91)	78.49 (84.80)	97.47 (98.57)	97.97 (98.75)

(c) Heavily censored (40%-60%)

λ_2	$n = 50$		$n = 100$	
	$\lambda_0 = 0$	$\lambda_0 = 1$	$\lambda_0 = 0$	$\lambda_0 = 1$
1.0	1.49 (2.29)	2.16 (2.82)	1.80 (2.61)	2.79 (3.64)
1.5	11.09 (16.02)	14.76 (19.79)	22.88 (29.12)	29.24 (35.85)
2.0	30.38 (39.76)	37.26 (46.75)	60.59 (68.79)	69.25 (76.49)
2.5	53.11 (63.73)	60.73 (70.27)	86.49 (91.57)	91.01 (94.72)

Note: The data were created using the uniform random number generator of Marsaglia, Zaman and Tsang (1990) and an algorithm of Friday and Patil (1977, Corollary 3.3). 10000 samples were used to obtain each entry in the table.

Figure 1

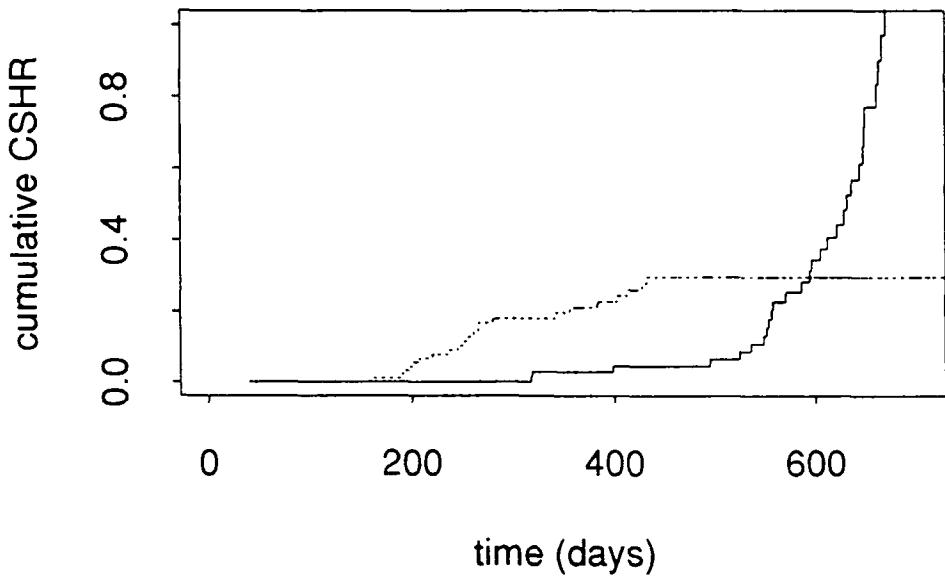


Figure 2

